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Hospital-onset adult invasive pneumococcal disease in Israel: Sicker patients, different pathogens

Ariel Kenig[a], Gili Regev-Yochay[b,**], Shirley Khakshoor[c], Ronit Cohen-Poradosu[d], Jihad Bishara[e], Daniel Glikman[f], Mirit Hershman-Sarafov[g], Ron Dagan[h], Oren Zimhony[i,*], for the IAIPD Research Group[1]

[a] Hadassah Medical Center, Affiliated to the School of Medicine, Hebrew University, Jerusalem, Israel
[b] Sheba Medical Center, Ramat-Gan, Affiliated to the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[c] Sheba Medical Center, Ramat-Gan, Israel
[d] Tel Aviv Medical Center, Affiliated to the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[e] Rabin Medical Center, Petach Tikva, Affiliated to the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[f] Galilee Medical Center, Naharia, Affiliated to The Faculty of Medicine in the Galilee, Tzfat, Israel
[g] Bnai Zion Medical Center, Affiliated to the Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
[h] Ben-Gurion University, Beer-Sheva, Israel
[i] Kaplan Medical Center, Affiliated to the School of Medicine, Hebrew University and Hadassah, Jerusalem, Israel

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ABSTRACT

Objectives: Invasive pneumococcal disease (IPD) usually has its onset in the community (CO-IPD), but it can commence following hospitalization (HO-IPD). This study compared HO-IPD and CO-IPD cases during the implementation of the pneumococcal conjugate vaccine (PCV) program for children in Israel.
Methods: This was a nationwide retrospective cohort study of adult (age >18 years) IPD patients covering the period from the implementation of the PCV7/13 program in 2009/2010 through 2015. HO-IPD and CO-IPD were defined as IPD with onset ≥4 and ≤2 days from admission, respectively. Patient characteristics, outcome measures, serotypes, and antimicrobial susceptibility were compared for the entire cohort, followed by a matched case–control analysis.
Results: The study included 114 patients with HO-IPD and 2180 with CO-IPD. After matching HO-IPD to CO-IPD patients by age, sex, and comorbidities, the mortality rate and discharge to long-term care facility rate were significantly higher for HO-IPD patients than for CO-IPD patients (44.6% vs. 26.3% and 26.5% vs. 8.2%, respectively). HO-IPD isolates were less often covered by PCV13 (39.6% vs. 49.0%) and pneumococcal polysaccharide vaccine PPSV23 (56.6% vs. 71.3%) and more often resistant to penicillin (9.3% vs. 3.6%), ceftriaxone (3.8% vs. 0.75%), and levofloxacin (9.3% vs. 0.8%).
Conclusions: HO-IPD was associated with higher morbidity and mortality than CO-IPD and was more often caused by non-vaccine serotypes (primarily non-PCV13 types) and antibiotic-resistant strains.

Introduction

Streptococcus pneumoniae is a major cause of morbidity and mortality. It is manifested in various infections including pneumonia, meningitis, and bloodstream infections (Drijkoningen and Rohde, 2014). Invasive pneumococcal disease (IPD) is defined as the isolation of *S. pneumoniae* from a normally sterile body fluid such as blood or cerebrospinal fluid (CSF) (Ludwig et al., 2012). In adults, the risk of IPD increases with age, especially in patients older than 65 years (Jansen et al., 2009; Ludwig et al., 2012).

* Corresponding author at: Infectious Diseases Unit, Kaplan Medical Center, Affiliated to the School of Medicine, Hebrew University and Hadassah, Jerusalem, Israel.
** Corresponding author at: Infection Prevention and Control Unit, Sheba Medical Center, Ramat-Gan, Affiliated to the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel.
E-mail addresses: kenig.ariel@gmail.com (A. Kenig), gili.regev@sheba.health.gov.il, gili.regev.y@gmail.com (G. Regev-Yochay), skhakshoor@gmail.com (S. Khakshoor), rcohenporadosu@gmail.com (R. Cohen-Poradosu), jihadb@clalit.org.il (J. Bishara), Daniel.glikman@biu.ac.il (D. Glikman), mirit.hershman@b-zion.org.il (M. Hershman-Sarafov), rdagan@bgu.ac.il (R. Dagan), oren_z@clalit.org.il (O. Zimhony).
[1] Members of the IAIPD Research Group are listed in the Appendix A.

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The 7-valent pneumococcal conjugate vaccine (PCV7) followed by the 13-valent vaccine (PCV13) have been implemented as part of national vaccination programs worldwide in the past two decades (Anon., 2000). In Israel, PCV7 was introduced into the pediatric national immunization plan (NIP) in July 2009 and was gradually replaced by PCV13 from November 2010. By June 2014, 91% of 24–35-month-old children had received three or more PCV13 doses (Regev-Yochay et al., 2017). This resulted in a marked overall decrease in IPD incidence in children (Ben-Shimol et al., 2012; Greenberg et al., 2015). Moreover, in adults, an approximate 20% decrease in all-serotype IPD incidence and an approximate 70% decrease in PCV7/13 serotype (vaccine type (VT)7/13) IPD was observed, due to an indirect effect (herd effect) (Cabaj et al., 2016; Regev-Yochay et al., 2017). However, parallel to the decline in VT13 IPD incidence, IPD caused by non-VT13 increased, partially blunting the beneficial effect of the vaccines (Regev-Yochay et al., 2017; Waight et al., 2015).

Hospital-onset IPD (HO-IPD, also termed nosocomial IPD) has been reported previously (Alvarez et al., 1986; Bouza et al., 2005; Canet et al., 2002; Lyytikainen et al., 2007; Paradisi et al., 2001; Rubins et al., 1999). HO-IPD patients suffer from a higher mortality rate (ranging from 31% to 74%) than patients with community-onset IPD (CO-IPD) (Alvarez et al., 1986; Lyytikainen et al., 2007). HO-IPD has been found to be more prevalent in patients with more comorbidities, contributing to the higher mortality rates (Bouza et al., 2005; Canet et al., 2002). However, large population-based datasets on the characteristics, microbiology, and outcomes of HO-IPD patients post-PCV implementation are missing.

This nationwide population-based study was conducted to compare patient characteristics, outcomes, and pneumococcal isolates between HO-IPD and CO-IPD patients, following the implementation of PCV7/13 vaccination in Israel.

Methods

Study period and population

A nationwide retrospective cohort study of population-based active surveillance, using the Israeli adult (age >18 years) IPD (IAIPD) active surveillance program database, was initiated on July 1, 2009, when PCV7 was introduced into the pediatric NIP. This report covers the period of July 1, 2009 through June 30, 2015, prior to the administration of PCV13 for Israeli adults. The database includes all IPD cases from 26 Israeli hospitals and one major outpatient health maintenance organization (Maccabi Health Service), and covers nearly all of the confirmed IPD cases in Israeli adults, as reported in detail previously (Ben-Shimol et al., 2012).

Study design

This was a retrospective cohort study based on the IAIPD database. The IAIPD group includes two researchers (a microbiologist and an infectious diseases physician) for each participating center responsible for data collection. The clinical data are recorded retrospectively for every prospective laboratory identified IPD case. This analysis covered 24 of the 27 medical centers for which medical files were available. Several isolate collecting methods were conducted: all invasive *S. pneumoniae* isolates are required by law to be reported and sent to the Israeli Ministry of Health Reference Laboratory. In addition, the current active surveillance has been using a capture–recapture method, where the IAIPD representatives in each of the 27 laboratories are contacted on a weekly basis by the study headquarters (at Soroka University Medical Center), as described previously (Ben-Shimol et al., 2012).

IPD was defined as the isolation of *S. pneumoniae* from blood or CSF. CO-IPD was defined as the isolation of *S. pneumoniae* before or within 2 days of admission. HO-IPD was defined as the isolation of *S. pneumoniae* at ≥4 days after hospitalization, to improve the distinction between HO-IPD and CO-IPD (cases diagnosed on the third day of hospitalization were excluded). The HO-IPD group was first compared to the CO-IPD group, followed by a matched case–control comparison between the groups.

Patient characteristics including age, sex, and comorbidities according to the US Centers for Disease Control and Prevention (CDC) definition for risk to IPD (CDC, 2015), the site of infection, and pathogen characteristics (proportion of strains with a serotype included in the pneumococcal vaccines and antimicrobial susceptibility) were compared. The outcomes analyzed were length of stay (LOS) since positive culture, rate of discharge to long-term care facility (LTCF) among those who were admitted from home, and all-cause in hospital mortality.

Laboratory testing

Serotyping was determined by the headquarters laboratory (Pediatric Infectious Disease Unit, Soroka University Medical Center) using the Quellung reaction (Staten Serum Institute, Copenhagen, Denmark). Susceptibility testing was conducted at the local laboratory of each medical center following the Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2017). The minimum inhibitory concentration (MIC) breakpoint for penicillin (μg/ml) was as follows: susceptibility <0.06, resistance ≥0.12.

Statistical analysis

Data comparison of the cohort, before matching, was conducted using the Chi-square test for categorical variables. A nested matched case–control analysis was then performed by matching HO-IPD to CO-IPD patients, in a ratio of one to four. Matching was based on the following variables: age group (18–50, 50–65, and ≥65 years), risk group, sex, and date of positive culture of CO-IPD within 6 months of HO-IPD positive culture (in order to adjust for temporal trends in serotype distribution). Risk groups were divided according to the CDC-defined IPD predisposing comorbidities, on which vaccine recommendations are based (CDC, 2015): (1) no risk, (2) at risk, including diabetes mellitus, chronic heart failure (CHF), chronic lung disease, cirrhosis, and alcoholism, and (3) high risk, including chronic kidney disease (CKD), infection with HIV, immunodeficiency (medically induced or innate), asplenic state, hematological or solid disseminated malignancy, bone marrow transplantation, and CSF leak or neurosurgery. Univariate analysis of the matched cases and controls was performed using univariate conditional logistic regression for categorical variables and mixed models with repeated measures for continuous variables. Predictors of mortality and of longer LOS were analyzed for the matched cohort using multivariate conditional logistic regression models. Adjusted odds ratios (OR), 95% confidence intervals (CI), and *p*-values were calculated. Statistical significance was set as $p \leq 0.05$. The statistical analysis was performed using SAS 9.4 software.

Results

Between the years 2009 and 2015, 2334 cases of IPD were recorded. All cases diagnosed on the third day of hospitalization ($n = 40$) were excluded. Initially, the characteristics of patients diagnosed on days 4 to 7 were compared to those of patients diagnosed on day 8 and onwards. Since no significant differences were found (Supplementary material, Table S1), all 114 patients with IPD diagnosed from day 4 onwards were grouped as HO-IPD cases (Figure 1).

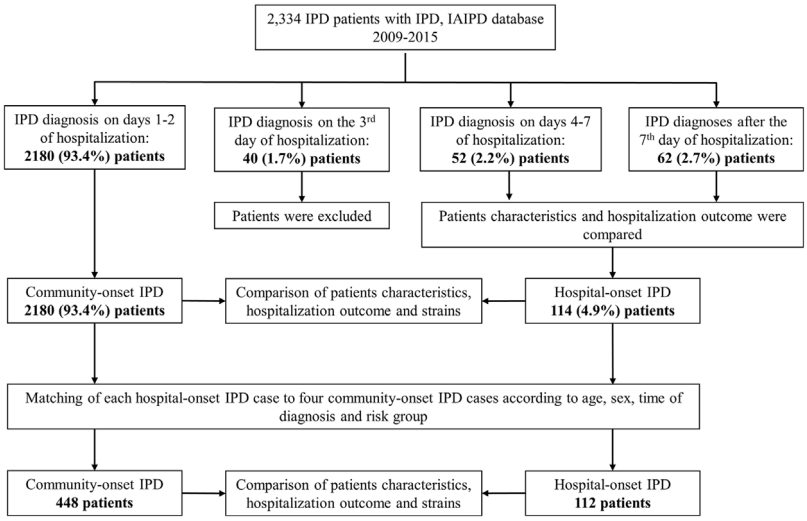

Figure 1. Research outline. Between 2009 and 2015, a total of 2334 patients with IPD were registered in the Israeli Adult IPD database. Patients were divided by day of IPD diagnosis. Forty patients diagnosed during their third day of hospitalization were excluded from the study; 2180 patients who had positive culture results during the first 2 days of hospitalization were defined as having CO-IPD. Patients with an IPD diagnosis on days 4–7 of hospitalization had similar characteristics and outcomes as patients with an IPD diagnosis at >7 days of hospitalization. Therefore, all patients with an IPD diagnosis from day 4 onwards were included in the HO-IPD group. Following comparison of HO-IPD and CO-IPD characteristics, HO-IPD and CO-IPD were matched in a 1:4 ratio according to age group, sex, risk group, and time of diagnosis, resulting in 112/114 HO-IPD matched cases. Abbreviations: CO-IPD, community-onset invasive pneumococcal disease; HO-IPD, hospital-onset invasive pneumococcal disease; IAIPD, Israeli Adult Invasive Pneumococcal Disease; IPD, invasive pneumococcal disease.

Characteristics of HO-IPD and CO-IPD patients

HO-IPD and CO-IPD patients differed in several characteristics (Table 1). A majority of the HO-IPD cases were male (64.0%, $p = 0.045$). The age distribution was similar, with more than 50% of both IPD groups being ≥65 years of age. CHF, metastatic malignancy, immunodeficiency, and bone marrow transplantation were significantly more prevalent in the HO-IPD group. All other comorbidities, except intravenous drug use and splenectomy, were also more prevalent among HO-IPD cases, but the difference did not reach statistical significance. Pneumonia was the major syndrome in both HO-IPD and CO-IPD, but it was significantly more often the identified cause for CO-IPD. Meningitis was also more common in CO-IPD, but the difference did not reach statistical significance. In contrast, bacteremia without a defined source was significantly more often associated with HO-IPD. The rate of mechanical ventilation was significantly higher in the HO-IPD group, although this included both patients who were ventilated before and after the onset of IPD. Intensive care unit (ICU) admission rates were similar in the two groups. The all-cause mortality rate during hospitalization was more than two-fold higher in HO-IPD patients (44.7% vs. 21.1%, $p < 0.0001$). Among patients who were admitted to the hospital from home, a higher proportion of HO-IPD patients were discharged to LTCFs.

Outcomes of patients with HO-IPD vs. CO-IPD

To compare the outcomes of HO-IPD and CO-IPD patients, a nested matched case–control analysis was conducted, with matching of comorbidities, age, and sex. The rates of the underlying medical conditions that comprise the CDC risk classification for IPD risk (CDC, 2015) were similar for HO-IPD and CO-IPD, except for CHF, which was significantly more common in the HO-IPD group. An asplenic state was more common in CO-IPD patients, while metastatic malignancy was more common in the HO-IPD group, albeit not significantly and with low rates (Table 2). Smoking and solid malignancy, which were both relatively common in the study cohort, were comparable, supporting the strength of the matching (Table 2) .

The mortality rate was 44.6% in the HO-IPD group compared to 26.3% in the CO-IPD matched group ($p = 0.0001$). The average length of stay since positive culture was 4.7 days longer in HO-IPD patients. The discharge to LTCF rate of HO-IPD patients was over three-fold that of CO-IPD patients. ICU admission and mechanical ventilation rates did not differ (Table 3). HO-IPD patients and their matched CO-IPD patients were treated with different antibiotics (Figure 2). The most common treatments for CO-IPD patients were ceftriaxone (73.8%), cefuroxime (19.1%), azithromycin (18.3%), and amoxicillin (17.4%). HO-IPD patients were most commonly treated with ceftriaxone (50.0%), vancomycin (36.2%), piperacillin–tazobactam (31.2%), and amoxicillin–clavulanate (10.5%).

Serotype differences in the nested matched analysis

Data on serotype were available for 106 HO-IPD cases and 439 CO-IPD cases. Seventeen cases were matched to 67 cases as 'no-risk', 24–103 as 'at-risk', and 65–269 as 'high-risk' for the HO-IPD and CO-IPD, respectively (Supplementary material, Table S2).

In the matched case–control analysis, a lower rate of VT13 serotypes was found in the HO-IPD vs. CO-IPD group, albeit not reaching statistical significance (39.6% vs. 49.0%, $p = 0.09$) (Table 4). There was no difference in the proportions of non-VT13 serotypes that are included in VT23 (VT23–13 serotypes). Yet, non-VT23 serotypes were significantly higher among HO-IPD vs. CO-IPD cases: 39.6% vs. 26.7% ($p = 0.008$). After stratifying by risk groups, this difference was particularly significant in patients at no risk or at risk: 6.6% vs. 1.8% ($p = 0.005$) and 11.3% vs. 6.4% ($p = 0.03$) for HO-IPD and CO-IPD, respectively; it did not reach significance among the high-risk group (Supplementary material, Table S2).

The proportions of certain serotypes differed significantly among HO-IPD patients compared to CO-IPD patients. The predominant serotypes (>4% of all matched serotypes) in patients with HO-IPD were 16F (11.3%) and 19A (8.5%), while in CO-IPD patients the predominant serotypes were 3 (8.9%), 19A (8.7%), 1 (6.2%), and 12F (5.7%). The individual serotypes that were significantly more prevalent among HO-IPD patients were serotypes 16F (11.3% vs. 4.33%, $p = 0.005$) and 23F (4.7% vs. 1.6%, $p = 0.049$) (Table 4).

Table 1
Univariate analysis of characteristics and hospitalization outcome of patients with hospital-onset and community-onset IPD.

Characteristic	No. (%) of patients HO- IPD (n = 114)	CO- IPD (n = 2180)	P value
Age group (years)			
< 50	20 (17.5)	530 (24.3)	
50 - 65	34 (29.8)	535 (24.5)	
> 65	60 (52.6)	1115 (51.2)	0.19
Sex			
Female	41 (36.0)	992 (45.6)	
Male	73 (64.0)	1185 (54.4)	**0.045**
Site of infection [a]			
Bacteremia without a source	42 (36.8)	357 (16.4)	<**0.0001**
Pneumonia	58 (50.9)	1553 (71.2)	<**0.0001**
Empyema	2 (1.8)	75 (3.4)	0.33
Meningitis	5 (4.4)	208 (9.5)	0.064
Sinusitis	0 (0.0)	27 (1.2)	0.23
Underlying medical condition			
High risk			
Chronic kidney disease	25 (21.9)	343 (15.7)	0.079
Metastatic malignancy	13 (11.4)	101 (4.6)	**0.0012**
Hematological malignancy	23 (20.2)	311 (14.3)	0.081
Immunodeficiency	27 (23.7)	271 (12.4)	**0.0005**
HIV infection	2 (1.8)	35 (1.6)	0.90
Asplenic state	1 (0.9)	66 (3.0)	0.18
Neurosurgery in the past	7 (6.1)	76 (3.5)	0.14
Bone marrow transplantation	9 (7.9)	65 (3)	**0.004**
At risk			
Chronic heart failure	33 (29.0)	322 (14.8)	<**0.0001**
Diabetes mellitus	34 (29.8)	583 (26.7)	0.47
Chronic lung disease	26 (22.8)	410 (18.8)	0.29
Alcoholism	4 (3.5)	68 (3.1)	0.82
Other			
Solid malignancy	17 (14.9)	271 (12.4)	0.44
Smoking	36 (31.6)	536 (24.6)	0.092
IVDU	1 (0.9)	55 (2.5)	0.28
Hospitalization outcome			
Death	51 (44.7)	459 (21.1)	<**0.0001**
ICU admission [b]	22 (19.3)	401 (18.4)	0.81
Ventilation [b]	38 (33.3)	446 (20.5)	**0.001**
Discharge to LTCF [c]	13 (26.0)	123 (7.8)	<**0.0001**

HIV, human immunodeficiency virus; ICU, intensive care unit; IPD, invasive pneumococcal disease; IVDU, intravenous drug user; LTCF, long-term care facility.
[*] $p < 0.05$.
[a] More than one infection source could have been attributed to each patient.
[b] Including ICU admissions and mechanical ventilation occurring before and after the IPD diagnosis.
[c] Applied to patients who arrived from home and survived hospitalization (1585 CO-IPD cases and 50 HO-IPD cases).

Differences in susceptibility to antibiotics in the nested matched analysis

The penicillin susceptibility profile was available for 104 HO-IPD isolates and 436 CO-IPD isolates. CO-IPD isolates were more often susceptible to penicillin (77.5% vs. 67.3%, $p = 0.022$), while intermediate susceptibility levels were similar (18.6% vs. 23.1%). The available HO-IPD isolates showed a significantly higher resistance to penicillin, ceftriaxone, and levofloxacin. The rate of erythromycin resistance was similar in the two groups (18%) (Table 5).

Independent predictors of mortality and longer LOS

In search of predictors of mortality and LOS, we conducted a logistic regression analysis with either VT13 (Table 6) or VT23, the site of infection, and HO-IPD vs. CO-IPD. The results of the two analyses were very close and showed that HO-IPD itself was an independent risk factor for both mortality and longer LOS. Meningitis was associated with longer hospitalization, although not with a higher risk of mortality. Serotype categories VT13 or VT23 were not found to be independent predictors of mortality and longer LOS.

Table 2
Underlying medical conditions for the matched case–control analysis.[a]

Characteristic	No. (%) of patients HO- IPD (n = 112)	CO- IPD (n = 448)	P value
Age group (years)			
< 50	20 (17.9)	80 (17.9)	
50 - 65	32 (28.6)	128 (28.6)	
>65	60 (53.6)	250 (53.6)	1.0
Sex			
Female	39 (34.8)	156 (34.8)	
Male	73 (65.2)	292 (65.2)	1.0
Underlying medical condition			
High risk	69 (61.6)	276 (61.6)	1.0
Chronic kidney disease	25 (22.3)	94 (21.0)	0.75
Metastatic malignancy	13 (11.6)	29 (6.5)	0.065
Hematologic malignancy	23 (20.5)	90 (20.1)	0.92
Immunodeficiency	26 (23.2)	90 (20.1)	0.47
HIV infection	2 (1.8)	17 (3.8)	0.29
Asplenic state	1 (0.9)	20 (4.5)	0.076
Neurosurgery in the past	6 (5.4)	24 (5.4)	1.0
Bone marrow transplantation	9 (8.0)	18(4.0)	0.07
At risk	26 (23.2)	104 (23.2)	1.0
Chronic heart failure	33 (29.5)	78 (17.41)	**0.004**
Diabetes mellitus	33 (29.5)	142 (31.7)	0.65
Chronic lung disease	26 (23.2)	97 (21.7)	0.72
Alcoholism	4 (3.6)	16 (3.6)	1.0
Other			
Solid malignancy	16 (14.3)	63 (14.1)	0.95
Smoking	35 (31.3)	122 (27.3)	0.40
IVDU	1 (0.9)	13 (2.9)	0.2

HIV, human immunodeficiency virus; IPD, invasive pneumococcal disease; IVDU, intravenous drug user.
[*] $p < 0.05$.
[a] Matched for comorbidities, sex, age, and date of positive culture.
[b] A patient could have more than one medical condition.

Table 3
Matched case–control analysis of in-hospital outcomes.[a]

Outcome	No. (%) of patients HO-IPD (n = 112)	CO- IPD (n = 448)	Odds Ratio (95% CI)	P value
Death	50 (44.6)	118 (26.3)	2.46 (1.55–3.91)	**0.0001**
ICU [a]	20 (17.9)	95 (21.2)	0.79 (0.46–1.38)	0.42
Ventilation [a]	36 (32.1)	106 (23.7)	1.52 (0.97–2.38)	0.069
Discharged to LTCFs [b]	13 (26.5)	25 (8.2)	5.17 (2.04–13.14)	**0.0005**
Mean LOS(days) [c]	16.2	11.5		**0.029**

CI, confidence interval; ICU, intensive care unit; IPD, invasive pneumococcal disease; LOS, length of stay; LTCF, long-term care facility; OR, odds ratio.
[*] $p < 0.05$.
[a] Matched for comorbidities, sex, age, and date of positive culture.
[b] Including ICU admissions and mechanical ventilation occurring before and after IPD diagnosis.
[c] Applied to patients who arrived from home and survived hospitalization (305 CO-IPD cases and 49 HO-IPD cases).
[d] Relates to length of stay from positive culture onwards, for patients who survived hospitalization.

Discussion

This study characterized HO-IPD for all IPD episodes in Israeli adults following the universal implementation of PCV7/13 vaccination for children. The proportion of HO-IPD among all IPD cases was 4.9%. Large population-based analyses of HO-IPD patient characteristics and outcomes are scarce. A Finnish population-based study, reported that HO-IPD comprised 10% of all IPD cases, but they included all cases detected at >48 h after

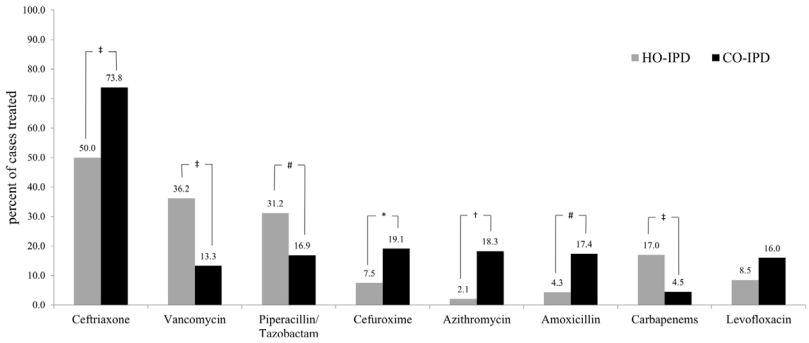

Figure 2. Antibiotic treatment for HO-IPD and CO-IPD cases. Treatment data were available for 94 HO-IPD cases and 420 CO-IPD cases. The data include all antibiotics that were used for each case, whether in parallel or successively. The commonly used antibiotics are presented. ‡$p < 0.0001$; †$p < 0.001$; #$p < 0.01$; *$p < 0.05$. Abbreviations: CO-IPD, community-onset invasive pneumococcal disease; HO-IPD, hospital-onset invasive pneumococcal disease; IPD, invasive pneumococcal disease.

Table 4
Serotype distribution among hospital and community-onset matched IPD cases.[a]

	No. (%) of patients			No. (%) of patients	
Serotype	**HO-IPD (n = 106)**	**CO-IPD (n = 439)**	**Serotype**	**HO-IPD (n = 106)**	**CO-IPD (n = 439)**
VT13 Serotypes	**42 (39.6)**	**215 (49.0)**	**non- VT23 serotypes [a]**	**42 (39.6)**	**117 (26.7)**
1 [a]	0 (0.0)	27 (6.2)	6C	3 (2.8)	10 (2.3)
3	4 (3.8)	39 (8.9)	6D	1 (0.9)	0 (0.0)
4	0 (0.0)	12 (2.7)	7B	1 (0.9)	4 (0.9)
5	3 (2.8)	16 (3.6)	9A	0 (0.0)	3 (0.7)
6A	4 (3.8)	9 (2.1)	10B	2 (1.9)	2 (0.5)
6B	3 (2.8)	9 (2.1)	10F	0 (0.0)	1 (0.2)
7F	2 (1.9)	13 (3.0)	11D	1 (0.9)	0 (0.0)
9V	3 (2.8)	11 (2.5)	13	0 (0.0)	2 (0.5)
14	4 (3.8)	19 (4.3)	15A	3 (2.8)	20 (4.6)
8C	1 (0.9)	4 (0.9)	16F [a]	12 (11.3)	19 (4.3)
19A	9 (8.5)	38 (8.7)	22A	0 (0.0)	1 (0.2)
19F	4 (3.8)	11 (2.5)	23A	0 (0.0)	3 (0.7)
23F [a]	5 (4.7)	7 (1.6)	23B	1 (0.9)	3 (0.7)
VT23-13Serotypes [b]	**22 (20.7)**	**107 (24.3)**	24F	2 (1.9)	10 (2.3)
2	1 (0.9)	2 (0.5)	31	2 (1.9)	5 (1.1)
8	1 (0.9)	18 (4.1)	33A [a]	2 (1.9)	0 (0.0)
9N	0 (0.0)	8 (1.8)	34	1 (0.9)	9 (2.1)
10A	3 (2.8)	5 (1.1)	35B	4 (3.8)	9 (2.1)
11A	4 (3.8)	12 (2.7)	35F	1 (0.9)	8 (1.8)
12F	2 (1.9)	25 (5.7)	38 [a]	4 (3.8)	5 (1.1)
15B/C	4 (3.8)	6 (1.4)	OMN	2 (1.9)	3 (0.7)
17F	1 (0.9)	4 (0.9)			
20	1 (0.9)	4 (0.9)			
22F	4 (3.8)	12 (2.7)			
33F	1 (0.9)	11 (2.5)			

CO-IPD, community-onset invasive pneumococcal disease; HO-IPD, hospital-onset invasive pneumococcal disease; IPD, invasive pneumococcal disease; VT13, vaccine-type 13; VT23, vaccine-type 23 (of PCV13 and PPSV23 vaccination, respectively).
[a]Matched for comorbidities, sex, age, and date of positive culture.
[b]Serotype proportion (%) that differed between HO-IPD and CO-IPD at a *p*-value <0.05.
[c]VT23–13 refers to serotypes that are included in VT23, but not included in VT13.

Table 5
Antibiotic resistance profile for hospital and community-onset matched IPD cases.[a,b]

Antibiotic susceptibility	HO-IPD % (n/N) of isolates	CO-IPD % (n/N) of isolates	P value
Penicillin resistance [a,b]	9.6 (10/104)	3.9 (17/436)	**0.012**
Ceftriaxone resistance [c]	3.9 (4/104)	0.7 (3/436)	**0.027**
Erythromycin resistance	18.6 (19/102)	17.9 (75/419)	0.86
Levofloxacin resistance	9.6 (7/73)	0.7 (2/297)	**0.0084**

IPD, invasive pneumococcal disease; MIC, minimum inhibitory concentration.
*$p < 0.05$.
[a]Matched for comorbidities, sex, age, and date of positive culture.
[b]Antibiotic resistance profile was not available for all cases.
[c]Intermediate resistance for penicillin was not included.
[d]MIC breakpoint for penicillin (μg/ml): susceptibility ≤0.06, resistance ≥0.12.
[e]MIC breakpoint for ceftriaxone (μg/ml): resistance ≥4.

Table 6
Conditional logistic regression model for mortality and longer LOS risk factors.

Characteristic	Mortality		Longer LOS[a]	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
HO-IPD vs. CO-IPD	2.58 (1.56–4.28)	0.0002*	3.33 (1.53–7.23)	0.002*
VT13 vs. non-VT13 serotype	0.92 (0.58–1.47)	0.73	1.00 (0.57–1.78)	0.99
Site of infection:				
Bacteremia vs. pneumonia	1.27 (0.76–2.12)	0.37	1.13 (0.56–2.27)	0.73
Meningitis vs. pneumonia	0.79 (0.33–1.92)	0.61	43.51 (5.55–340.95)[b]	0.0003*

OR, odds ratio; CI, confidence interval; CO-IPD, community-onset invasive pneumococcal disease; HO-IPD, hospital-onset invasive pneumococcal disease; LOS, length of stay.
*$p < 0.05$.
[a]Longer LOS defined as 8 days of hospitalization or more, since positive blood/cerebrospinal fluid culture.
[b]The large CI expresses uncertainty due to the high percentage of longer LOS among meningitis patients (90%).

admission (Lyytikainen et al., 2007). We used an IPD onset of ≥4 days from admission to define HO-IPD in order to exclude community cases with delayed culture (Lyytikainen et al., 2007). After matching for comorbidities that were similar for the matched HO-IPD and CO-IPD cases, HO-IPD was still associated with a higher in-hospital mortality rate (44.6%) relative to CO-IPD, in accordance with the results of other studies (Bouza et al., 2005; Rubins et al., 1999).

Previous studies have used the terms nosocomial or healthcare-acquired IPD (Bouza et al., 2005; Canet et al., 2002; Garner et al., 1988; Lyytikainen et al., 2007). We chose the term HO-IPD because the most likely source of IPD following admission is the invasion of endogenous pneumococcal strains that are colonizing the upper respiratory tract for an unknown time prior to the onset of IPD. Moreover, the exclusion of incubation of an implicated infection during admission, a prerequisite for nosocomial infection (Garner et al., 1988), is impossible. Nosocomial outbreaks of *S. pneumoniae* are rare and occur mainly in the institutional setting. A systematic review identified only 42 outbreaks between the years 1980 and 2006 (Ihekweazu et al., 2010). Our series encompassed sporadic cases from many centers over a 6-year period; therefore, the role of nosocomial transmission and outbreak in this study is probably negligible.

Previous studies have attributed the higher mortality of HO-IPD cases to an increased prevalence of predisposing factors for IPD among hospitalized patients (Bouza et al., 2005; Canet et al., 2002). HO-IPD patients suffer from higher rates of underlying medical conditions, which constitute a risk for IPD and include CHF, malignancy, immunodeficiency state, and chronic lung disease (Lyytikainen et al., 2007). Diabetes mellitus, chronic liver disease, and alcoholism have also been reported to be associated with HO-IPD (Bouza et al., 2005; Lyytikainen et al., 2007; Rubins et al., 1999). In one study, the majority of HO-IPD patients had a fatal or ultimately fatal medical condition while diagnosed with IPD (Bouza et al., 2005). Similarly, in the present study, higher rates of comorbidities were found in the HO-IPD patients. Thus, it is not surprising that mortality is higher in these patients.

However, it was found that even after matching for risk groups to IPD (i.e., for comorbidities), the difference in mortality between HO-IPD and CO-IPD patients only narrowed slightly and remained significant.

It is assumed that hospitalization, which is often prolonged in HO-IPD patients due to increased comorbidities, contributes to the mortality difference between HO-IPD and CO-IPD patients. First, hospitalization by itself conditions for an increased mortality regardless of IPD (Krumholz, 2013). Second, the hospital environment with its wide antimicrobial usage exerts selective pressure that might result in the acquisition of less virulent, more often antimicrobial-resistant strains. HO-IPD caused by these different serotypes then emerges due to the vulnerability of frail hospitalized patients. The finding that less virulent non-VT23 serotypes (Yildirim et al., 2010) were more prevalent in patients with HO-IPD than in those with CO-IPD, but mainly in the subgroups with fewer comorbidities (non-risk or at -risk groups), supports this hypothesis.

A previous study demonstrated that non-VT13 strains caused higher rates of bacteremia without a source and a tendency towards higher mortality from non-VT13 strains (Browall et al., 2014). Yet in the present study, the non-VT13 or VT13 strain difference did not have an independent effect on the risk of mortality or longer LOS. Finally, when IPD ensues during hospitalization, the symptoms may be masked by those of the other syndromes for which the patient has been hospitalized, causing a possible delay in diagnosis. HO-IPD patients were more frequently diagnosed with pneumococcal bloodstream infections with no apparent source, reflecting the difficulty reaching a specific diagnosis in sepsis-prone, hospitalized patients with other active illnesses. It is hypothesized that this diagnostic difficulty could have resulted in delayed appropriate therapy for HO-IPD, further worsening the outcomes of HO-IPD patients.

It had been reported that specific serotypes are more likely to be associated with invasive disease or antibiotic resistance (Brueggemann et al., 2004; Song et al., 2012). A study of serotype prevalence in adults hospitalized with non-invasive community-acquired pneumococcal pneumonia showed that less invasive serotypes were significantly associated with increasing age and comorbidity and with higher 30-day mortality compared with highly invasive serotypes (Bewick et al., 2012). Similarly, we have previously shown that IPD in chronically ill patients is more frequently caused by supposedly less invasive, non-VT serotypes (Regev-Yochay et al., 2015; Regev-Yochay et al., 2013).

Thus, the finding that non-VT serotypes were more frequently detected in HO-IPD and could adversely affect the outcome is in accordance with these studies. The predominance of serotype 16 F, a relatively non-invasive serotype (Yildirim et al., 2010), amongst the non-VT serotypes in HO-IPD compared to the non-VT serotypes implicated in CO-IPD has not been described previously (Cui et al., 2017). We propose that this finding further supports the suggestion that hospitalization in itself is an independent risk factor for mortality.

Frequent and longer hospitalizations with past antibiotic exposure probably affect nasopharyngeal colonization with specific serotypes. The proportion of VT23 serotypes in this study (56.5%) is lower than the reported rate of 71.5–78% in previous studies (Bouza et al., 2005; Lyytikainen et al., 2007). This difference might be related to geographical and temporal trends, as well as to the effect of PCV7/13 implementation in the pediatric NIP on adult IPD, as reported previously (Cabaj et al., 2016; Regev-Yochay et al., 2017; Waight et al., 2015). Since our study relates to patients diagnosed following PCV7/PCV13 implementation, it is plausible to assume that vaccination affected the serotypes causing HO-IPD in a similar manner.

The rates of penicillin, ceftriaxone, and levofloxacin resistance were significantly higher in HO-IPD isolates. However, the increased rates of antibiotic resistance probably made a minor contribution to the higher mortality rate in HO-IPD, as the total number of resistant strains in this study was low. Moreover, the HO-IPD patients herein were more often treated with vancomycin and carbapenems, to which pneumococci are universally susceptible (Kalil et al., 2016), as empiric therapy for hospital-acquired infections. Thus the worse outcome for HO-IPD was not due to inadequate empiric antibiotic therapy. It is assumed that the delayed diagnosis and onset of any antimicrobial treatment could have resulted in the worse outcome for HO-IPD patients.

This study has several limitations: first, only the in-hospital mortality was assessed and there were no follow-up data on 30-day mortality. However, it is unlikely that patients would have been discharged with a severe active infection, thus it can be assumed that most of the IPD-related deaths were included. Second, the matching procedure adjusted for some but not all of the patient characteristics, such as hospitalization history, procedures, and past antibiotic therapy, which might affect the susceptibility to pneumococcal acquisition of different pneumococcal serotypes and subsequent invasive infection. Nevertheless, the nested matched analysis did include the most important predictors of severe disease: age and comorbidities. Third, since the data collection began with the implementation of PCV7, this study did not include the strain distribution of HO-IPD in the pre-PCV era. This limits the assessment of the impact of PCV7 vaccination on the rate of HO-IPD serotypes. Last, the timing of actual administration of antibiotic therapy was not matched with the isolation of the strain implicated in IPD, thus limiting the assessment of appropriate therapy on the outcome.

In conclusion, HO-IPD patients suffered from higher rates of comorbidities, mainly metastatic malignancies, CHF, and immunodeficiency. HO-IPD was more often caused by non-VT serotypes, particularly non-VT23 serotypes with higher rates of antibiotic resistance, compared to CO-IPD. Yet, a significant proportion of HO-IPD cases were still attributed to VT13 and VT23 serotypes; thus the current vaccination policy based on risk groups as endorsed by the CDC (CDC, 2015) is expected to diminish the risk of HO-IPD to some extent.

Mortality was significantly higher in HO-IPD patients, even after adjusting for comorbidities. Whether this is due to an independent risk of being hospitalized or due to delayed diagnosis needs further investigation.

Clinicians should consider IPD in the differential diagnosis of hospital-acquired infections. The use of urinary pneumococcal antigen (Sinclair et al., 2013) and rapid molecular diagnostic methods (Timbrook et al., 2017) in cases of pneumonia and sepsis of unknown origin in hospitalized patients may expedite the diagnosis of HO-IPD and could direct earlier focused therapy for HO-IPD.

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Ethical approval

Not required.

Conflict of interest

G.R.Y. has served as a consultant for Neopharm and Pfizer. R.D. has received grants/research support from Berna/Crucell, Wyeth/Pfizer, MSD, and Protea; has been a scientific consultant for Berna/Crucell, GlaxoSmithKline, Novartis, Wyeth/Pfizer, Protea, and MSD; has been a speaker for Berna/Crucell, GlaxoSmithKline, and Wyeth/Pfizer; and is a shareholder of Protea/NASVAX.

Appendix A.

The IAIPD study investigators (2015): Study PI: Gili Regev-Yochay (Sheba Medical Center, Ramat-Gan & Tel-Aviv University, Tel-Aviv). IsraNIP Project PI: Ron Dagan (Ben-Gurion University, Beer-Sheva). Co-investigators: Marc Assous (Shaare Zedek Medical Center, Jerusalem), Haim Ben-Zvi, Jihad Bishara (Rabin Medical Center, Pethah-Tikva), Rita Bardenstein (Kaplan Medical Center, Rehovot), Larissa Brik (Asaf Harofe Medical Center, Zrifin), Bibiana Chazan (Ha-Emek Medical Center, Afula), Michal Chowers (Meir Medical Center, Kfar Saba), Ronit Cohen-Poradosu, Talia Finn (Tel-Aviv Medical Center, Tel-Aviv), Alicia Embon (Barzilai Medical Center, Ashkelon), Sarit Freimann (Hillell Yaffe Medical Center, Hedera), Yuval Geffen (Ramabam Medical Center, Haifa), Danny Glikman (Western Galilee Hospital, Nahariah), Mirit Hershman (Bnai Zion Medical Center, Haifa), Valery Istomin (Hillel Yaffe Medical Center, Hedera), Michal Katzir (Meir Medical Center, Kfar Saba), Yoram Kennes (HaEmek Medical Center, Afula), Shirley Khakshoor (Sheba Medical Center, Ramat-Gan), Camellia Khoury-Assi (French Hospital, Nazzeret), Mandelbaum Sari (Laniadu Medical Center, Natanya), Yasmin Maor (Wollfson Medical Center, Holon), Danny Miron (Ziv Medical Center, Safed), Ilana Oren (Rambam Medical Center, Haifa), Yosi Paitan (Meir Medical Center, Kfar Saba), Yael Paran (Tel-Aviv Medical Center, Tel-Aviv), Nehama Peled (Soroka University Medical Center, Beer-Sheva), Avi Peretz (Poriah Medical Center, Tiberius), Nurit Porat (Soroka University Medical Center, Beer-Sheva), Israel Potasman (Bnai Zion Medical Center, Haifa), Galia Rahav (Sheba Medical Center, Ramat-Gan), Hagai Rechnitzer (Ziv Medical Center, Safed), Klaris Reisenberg (University Medical Center, Beer-Sheva), Shifra Sela (Western Galilee Hospital, Nahariah), David Schwartz (Tel Aviv Medical Center, Tel-Aviv), Orna Schwartz (Wollfson Medical Center, Holon), Pninit Shaked-Mishan (Carmel Medical Center, Haifa), Yehudit Sheindler (Maayanei Hayeshua Hospital, Bnei Brak), Gill Smollan (Sheba Medical Center, Ramat-Gan), Itzhak Srugo (Bnai Zion Medical Center, Haifa), Michal Stein (Wollfson Medical Center, Holon), Jacob Strahilevitz (Hadassah-Hebrew University Medical Center, Jerusalem), Olga Sverdlob (Maccabi Healthcare Services, Rehovot), Violetta Temper (Hadassah-Hebrew University Medical Center, Jerusalem), Evgenia Tsyba (Barzilai Medical Center, Ashkelon), Yonit Wiener-Well (Shaare Zedek Medical Center, Jerusalem), Gabriel Weber (Carmel Medical Center, Haifa), Miriam Weinberger (Assaf Harofeh Medical Center, Tzrifin), Oren Zimhony (Kaplan Medical Center, Rehovot).

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.06.013.

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